Full Text OD-97-006

ACUPUNCTURE TREATMENT FOR OSTEOARTHRITIS
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P.T.
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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: August 17, 1997
Application Receipt Date: September 19, 1997

PURPOSE

The Office of Alternative Medicine (OAM) was mandated by Congress in 1991 and permanently established within the Office of the Director, National Institutes of Health (NIH), through the National Institutes of Health Revitalization Act of 1993 (Public Law 103-43, Section 209). The mission of the OAM is to encourage and support the investigation of complementary and alternative medical (CAM) practices, with the ultimate goal of integrating validated alternative medical practices into health and medical care.

The OAM and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) seeks, with this RFA, to initiate a clinical trial of acupuncture for the treatment of osteoarthritis (OA) of the knee by experienced investigators who have the unique technical capabilities to study acupuncture in a clinical setting. This proposal has the potential to address the efficacy of acupuncture for the treatment of OA.

HEALTHY PEOPLE 2000

The Public Health Service is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," an initiative for setting national health policy and priorities. Although Healthy People 2000 does not currently specify a CAM or acupuncture objective, this RFA involves priority areas within the Healthy People 2000 objectives, such as the area of chronic disabling conditions. Applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through

the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402-9325 (Telephone: 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted only by domestic and foreign for-profit and not-for-profit organizations, public and private organizations such as universities, colleges, hospitals, laboratories, units of State or local governments, Federally recognized Indian Tribal organizations, and eligible agencies of the Federal government. Applications from minority and women investigators and persons with disabilities are encouraged.

MECHANISM OF SUPPORT

This RFA will use the cooperative agreement (U01) mechanism. The cooperative agreement is an assistance mechanism in which it is anticipated that the NIH will have substantial involvement with the recipient during the performance of the planned activity. The nature of the NIH's involvement is described under the "Terms and Conditions" of the award. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant/awardee.

The total project period for applications submitted in response to the present RFA may not exceed five years, although a three to four year study is anticipated. The anticipated award date is April 1, 1998. This RFA is a one-time solicitation. Future unsolicited competitive continuation applications will compete with all other investigator-initiated research applications and be peer-reviewed by a study section in the Division of Research Grants (DRG), NIH.

FUNDS AVAILABLE

Depending upon the scope of work, up to $500,000 (total costs) per year is available to support this RFA. It is expected that one award will be made. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of the award will vary also. Although this program is provided for in the financial plans of the OAM and the NIAMS, awards made pursuant to this RFA will be contingent on the continued availability of funds for this purpose.

RESEARCH OBJECTIVES

Background

Osteoarthritis (OA) is a common, costly and potentially disabling disease of joints that affects more than 16 million Americans at an economic cost in excess of $8 billion, annually. Pain and limitation of motion are its major manifestations. Since OA cannot be cured, management of OA is dependent on adequate pain control and maintaining or improving mobility. The analgesics and anti-inflammatory medications commonly prescribed to treat OA pain may not be effective for all individuals and sometimes produce side effects. A variety of surgical procedures may be recommended depending upon disease severity and patient complaints.

Since its reintroduction to the West in 1972, acupuncture has been subject to scientific investigation resulting in a substantial body of literature. Some of this literature suggests that acupuncture may provide substantial pain relief for OA without producing the side effects associated with conventional medications. Unfortunately, the few studies that have specifically examined the efficacy of acupuncture for the treatment of OA have produced contradictory results. Part of the discrepancy in these studies has been the difficulty in designing adequate control groups, differences in the length and mode of the acupuncture treatment, inadequate endpoints and insufficient sample sizes.

Purpose of Proposed Research

The purpose of the proposed study is to initiate a clinical efficacy trial of acupuncture for OA of the knee. Also examined will be the safety and acceptability of acupuncture. Research activities will be conducted by clinical investigators skilled in acupuncture and knowledgeable about the diagnosis, staging and clinical management of OA. The ultimate goal is to determine the efficacy of acupuncture for OA and extend knowledge about its utility for this condition.

Research Plan

Objectives of the RFA will be met through the initiation of a full-scale, randomized, controlled trial to test the efficacy of acupuncture for the treatment of OA of the knee. It is expected that the trial will compare acupuncture needling to sham needling (placebo control). Additional treatment comparisons may be added if it/they are solidly supported by the research literature and/or compelling preliminary data. Potential applicants should understand that additional treatment comparisons will add to the cost of the overall study and enhance problems with patient recruitment and project management. All applicants should demonstrate their ability to manage a complex trial, and provide a detailed patient recruitment plan, a detailed data management plan, and sample size and power calculations. These criteria are particularly important for those applicants who propose to expand the trial beyond two arms. In addition, it is important to

evaluate any side effects or complications of treatment. The appropriate acupuncture needling treatment, placebo control and other treatment comparisons will be chosen based on review of the literature and standards of practice.

The rationale for the proposed patient population should include disease severity and other inclusion/exclusion criteria. It is recommended that the study population include both men and women with either unilateral and bilateral knee OA of at least mild severity. Subjects who have previously used acupuncture for any illness, including OA, may be included in the study; however those subjects who have failed acupuncture treatment for OA should be excluded from the study. Plans for patient follow-up and choices of outcome measures (primary and secondary) should be well-defined and clearly justified. Outcome measures could include, but are not limited to: 1) pain assessment; 2) functional status; 3) health status/quality- of-life indicators and 4) side effects 5) health care utilization (e.g., increased or decreased use of non-steroidal anti-inflammatory drugs or office visits). Selected outcome measures and criteria for meaningful clinical improvement must be specifically addressed in the application.

The study should consist of four phases: 1) an initial phase during which the protocol is finalized (e.g., study procedure, data collection manuals, data management, training, establishment of the DSMC, etc.) after consultation with the NIAMS Program Officer and the OAM Project Consultant; 2) a recruitment period; 3) a period of intervention and follow-up; and 4) data analysis and dissemination. Applicants must demonstrate the ability to recruit and randomize the required number of study participants, be able to implement the various study procedures, and maintain high rates of follow-up during the course of the trial. It will be particularly important to minimize the number of self-medicating patients. Applicants should pay special attention to the choice of an appropriate placebo, the issue of masking, and subject inclusion and exclusion criteria. If preliminary data are not available, the proposal should include a pilot phase to validate these items.

To assure adequate statistical power, the clinical trial design should include an adequate number of participants and should be of sufficient duration to address the study questions of efficacy, safety and acceptability, as well as any other secondary research questions. To this end, biostatistics and clinical trial design expertise should be included during the planning and design of the study. Study size and duration will vary according to specific study hypotheses, target population and endpoints; as such, the study size and duration should reflect both the choice of outcome measures and the predicted effect sizes.

Any secondary objectives and scientific approaches included by the applicant should reflect the creativity and capability of the investigators. This RFA provides an opportunity for clinical investigators within an institution or consortia of institutions to initiate or expand a program on acupuncture research.

All costs required for these studies must be included in the application and must be fully justified. These costs include quality control, data management and data analysis, study monitoring, and travel.

Applications funded under this RFA will be supported through the cooperative agreement (U01) mechanism. An assistance relationship will exist between the NIH and the awardees to accomplish the research objectives. As described more fully below, the recipients will have primary responsibility for the development and performance of the activity.

SPECIAL REQUIREMENTS

Definitions

NIAMS Program Officer: the NIAMS Program Staff official having responsibility for the stewardship and monitoring of the award. In addition, the NIAMS Program Officer will participate as a Project Scientist in cooperation with the OAM Project Consultant.

OAM Project Consultant: the OAM Project Consultant will provide scientific/programmatic assistance to the Awardee as noted in the terms and conditions of the award, and will provide input to the NIAMS Program Officer concerning normal stewardship functions.

Data Safety and Monitoring Committee: the committee composed of external, nonparticipating scientists appointed by the Principal Investigator to monitor patient safety, conduct data audits, and document progress to the NIAMS Program Officer and the OAM Project Consultant.

General Issues

An independent Data and Safety Monitoring Committee (DSMC) will be a required component of the study. The DSMC will monitor response data to ensure patient safety. Assessment of the adequacy of the DSMC will be an important review criterion. Applicants should not name DSMC members until an award is made; however, within the application, they should specify the process by which DSMC members will be identified. Although identified by the applicant after

consultation with the NIAMS Program Officer and the OAM Project Consultant, the DSMC will be appointed by the applicant's institution and report to the Director of NIAMS through the NIAMS Program Officer. An operating budget for the DSMC shall be specified and justified in the application.

The Awardee(s) will be required to submit semiannual progress reports to NIAMS. These reports should include recruitment data, indices of quality control, reports of significant side effects or morbidity and changes in the protocol. Such reports are in addition to the annual awardee noncompeting continuation progress report. The Data Safety and Monitoring Committee may require additional information. The Awardee(s) also will be requested to present a final oral report to the Advisory Councils of both the OAM and the NIAMS.

The Awardee(s) will be expected to disseminate the research findings in a timely manner through peer-reviewed publications.

TERMS AND CONDITIONS OF THE AWARD

These special Terms and Conditions of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, HHS grant administration regulations in 45 CFR part 74 and 92, and other HHS, PHS and NIH grant administration policy statements.

The administrative and funding instrument used shall be a cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism) in which substantial NIAMS and OAM scientific and/or programmatic involvement with the Awardee is anticipated during performance of the activity. Under the cooperative agreement, the purpose of the NIAMS and the OAM is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity.

Consistent with the above concept, the dominant role and prime responsibility for the activity reside with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees, the NIAMS Program Officer and the OAM Project Consultant.

Under the cooperative agreement, a relationship will exist between the recipient of these awards, the NIAMS and the OAM, in which the performers of the activities are responsible for the

requirements and conditions described below, and agree to accept program assistance from the NIAMS Program Officer and OAM Project Consultant.

A. Awardee(s) Rights and Responsibilities.

The Awardee(s) is responsible for:

1. Research design and protocol development, including definition of objectives and approaches, planning, implementation, participant recruitment and follow-up, data collection, quality control, interim data and safety monitoring, final data analysis and interpretation, and publication of results.

2. Establishing an external Data Safety and Monitoring Committee to review data. The Principal Investigator, after consultation with the NIAMS Program Officer and the OAM Project Consultant, will name external, nonparticipating investigators to serve as members on a Data Safety and Monitoring Committee and schedule meetings periodically. The NIAMS Program Officer and OAM Project Consultant will be non-voting members.

3. Functioning as the scientific coordinator for the protocol and assuming responsibility for developing and monitoring the protocol. All proposed protocol modifications will be submitted by the Principal Investigator to the NIAMS Program Officer and OAM Project Consultant, for review and approval, subject to negotiation with the Awardee(s).

4. Implementing the data collection method and strategy.

5. Establishing mechanisms for quality control and monitoring. Awardees are responsible for ensuring accurate and timely assessment of the progress of their study, including development of procedures to ensure that data collection and management are: (1) adequate for quality control and analysis; (2) for clinical trials, as simple as appropriate in order to encourage maximum participation of physicians and patients and to avoid unnecessary expense; and (3) sufficiently staffed.

6. Establishing procedures to comply with the requirements of 45 CFR Part 46 for the protection of human subjects. The Principal Investigator is responsible for obtaining approval from the Institutional Review Board (IRB) prior to enrolling patients, and, once enrollment has commenced, from the IRB, the NIAMS Program Officer and the OAM Project Consultant prior to changing the protocol.

7. The Awardee(s) will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current DHHS, PHS and NIH policies.

B. NIH Staff Responsibilities

It is expected that the dominant role and prime responsibility for the activity will reside with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardee(s), the NIAMS Program Officer and the OAM Project Consultant concerning specific scientific and/or analytic issues as described below. However, the NIAMS Program Officer will retain overall administrative responsibility for the award and will be the contact point for all facets of interactions with the awardee(s) concerning such issues.

NIH Program Staff responsibilities will include:

1. The NIAMS Program Officer and OAM Project Consultant will attend meetings of the Data Safety and Monitoring Committee as non-voting members. The NIAMS and OAM retain, as an option, the right to conduct periodic external review of progress.

2. The NIAMS Project Officer will provide scientific/technical assistance primarily on issues concerning osteoarthritis and other items indicated in this section. The OAM Project Consultant will provide scientific/technical assistance primarily on issues concerning acupuncture and other items indicated in this section.

3. If applicable, the NIAMS Program Officer and OAM Project Consultant will serve as a resource with respect to other ongoing NIAMS and OAM activities that may be relevant to the protocol to facilitate compatibility and avoid unnecessary duplication of effort.

4. The NIAMS Program Officer and OAM Project Consultant will assist in the design and coordination of research activities for Awardees as elaborated below:

a. Assist by providing advice in the management and technical performance of the investigations.

b. Assist through participation in meetings/correspondence with the research team. With the agreement of the Principal Investigator, the NIAMS Program Officer and OAM Project Consultant may assist in the design, development, and coordination of the research or clinical protocol, in the

statistical evaluations of data, in the preparation of questionnaires and other data recording forms, and in the publication of results.

c. Assist with the review and approval of protocols to ensure they are within the scope of peer review and also for safety considerations, as required by Federal regulations. The NIAMS Program Officer and OAM Project Consultant will monitor protocol progress, and may request that a protocol study be closed to accrual for reasons including: a) an accrual rate insufficient to complete study in a timely fashion; b) accrual goals met early; c) poor protocol performance; d) patient safety and regulatory concerns; e) study results that are already conclusive; and f) emergence of new information that diminishes the scientific importance of the study question.

d. Review and provide advice regarding the establishment of mechanisms for quality control and study monitoring.

5. The NIAMS Program Officer, in conjunction with, or upon recommendations of, the OAM Project Consultant, reserves the right to curtail or terminate the study and award in the event of:

a) failure to implement the collaborative protocol in a timely fashion;

b) substantial shortfall in patient recruitment, follow-up, data reporting, quality control, or other major breech of the protocol;

c) substantive changes in the agreed upon protocol with which the NIAMS and the OAM do not concur;

d) reaching a major study end point substantially before schedule with persuasive statistical significance; or

e) human subject ethical issues that dictate premature termination.

6. Reporting of the study findings. The NIAMS and OAM will have access to and may periodically review all data generated under an award. NIH policies governing possible co-authorship of publications with NIH staff will apply in all cases. In general, to warrant co-authorship, NIH staff must have contributed to the following areas: (a) design of the concepts or experiments being tested; (b) performance of significant portions of the activity; and preparation and authorship of pertinent manuscripts.

C. Collaborative Responsibilities

In addition to the interactions defined above, the NIAMS Program Officer, OAM Project Consultant and Awardees shall share responsibility for the following activity:

Data Safety and Monitoring Committee.

This committee is organized by the Principal Investigator, the NIAMS Program Officer and the OAM Project Consultant and is the main oversight body of the clinical trial. The Data Safety and Monitoring Committee has primary responsibility to review progress, monitor patient accrual, data management, and patient safety, and cooperate on the publication of results. The Data Safety and Monitoring Committee will document progress in written reports to the Director of NIAMS through the NIAMS Program Officer, and will provide periodic supplementary reports to designated NIH staff upon request.

The Data Safety and Monitoring Committee will be composed of external, nonparticipating peer Investigators, including those of data coordinating/statistical centers, if any, and the NIAMS Program Officer and OAM Project Consultant. An initial meeting of the Data Safety and Monitoring Committee will be convened by the Principal Investigator early after an award is made. The final structure and membership of the Data Safety and Monitoring Committee will be established at the first meeting. The Principal Investigator will not be a member or routine attendee of the Committee after the first meeting of the Committee. The NIAMS Program Officer and OAM Project Consultant will have nonvoting membership on the Committee, and as appropriate, its subcommittees. Such a Committee usually will meet at least yearly.

A Chairperson, other than the NIH representatives, will be selected by a vote of the members. The Chairperson is responsible for coordinating the Committee activities, for preparing meeting agendas, and for scheduling and chairing meetings.

E. Arbitration

Any disagreement that may arise on scientific/programmatic matters (within the scope of the award), between award recipients and the NIH may be brought to arbitration. An arbitration panel will be composed of three members -- one selected by the awardee, a second member selected by NIAMS and OAM, and the third member selected by the two prior selected members. These special arbitration procedures in no way affect the awardee's right to appeal an adverse action

that is otherwise appealable in accordance with PHS regulations at 42 CFR Part 50, Subpart D, and HHS regulations at 45 CFR Part 16.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided, that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations) which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 9, 1994 (CFR 59 11146-11151), and reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from the program staff or contact person listed below. Program staff may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Prospective applicants are asked to submit, by August 17, 1997, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the title ACUPUNCTURE TREATMENT FOR OSTEOARTHRITIS and the RFA number: OD-97-06.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows OAM and NIAMS staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to:

Dr. Tommy Broadwater
Extramural Program
NIAMS
Natcher Building, Room 5AS-25U
45 Center Drive MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX: (301) 480-4543

APPLICATION PROCEDURES

To apply for this RFA, a research grant application form, PHS Form 398 (rev. 5/95) must be used. Forms are available at most institutional offices of sponsored research, from the NIAMS and OAM program administrators named below or from the World Wide Web at: http://grants.nih.gov/grants/funding/funding.htm.

Prior to writing the application, applicants should carefully read the instructions provided with PHS Form 398 and this RFA.

The RFA label available in the PHS 398 application package must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application. In addition, the RFA title and number must be typed on line two of the face page of the application form and the YES box must be marked.

Submit a typewritten, signed original of the application, three signed photocopies, and the completed checklist in one package to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, it is also required to mail one additional complete, signed copy of the application to each of the following RFA program administrators:

Richard L. Nahin, Ph.D., M.P.H.

NIH Office of Alternative Medicine
9000 Rockville Pike
Bldg. 31, Room 5B-38
Bethesda, MD 20892-2182

James Panagis, M.D., M.P.H.
Medical Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building Room 5AS-37K - MSC 6500
Bethesda, MD 20892-6500
Tel: 301-594-3513
Fax: 301-480-4543
E-mail: panagis@ep.niams.nih.gov

Applications must be received by September 19, 1997. If an application is received after the date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this announcement that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such an application must follow the guidance in the PHS Form 398 application instructions for the preparation of revised applications, including an introduction addressing the previous critique.

Preparation of the Application

The general instructions provided in PHS-398 for the preparation of applications must be used. Because the "Terms and Conditions of Award" will be included in all awards issued as a result of this RFA, it is critical that each applicant provides specific plans for responding to the terms and conditions of award and requirements stated in the RFA. Plans must take into account NIH staff involvement, as well as how all the responsibilities of Awardees will be fulfilled.

The following items apply to all applications:
1. Clinical trial designs should include an adequate number of participants and should be of sufficient duration to assure statistical power to address the study questions of efficacy, long-term safety and acceptability. To this end, biostatistics and clinical trial design expertise should be included from the first efforts in study planning and design.

2. A rationale for selection of the target patient cohort and an estimate of the number of participants required to complete the clinical study should be provided. Criteria and calculations used to estimate sample size should be included. The patient cohort should be described and its selection justified. The cohort should be defined, as appropriate, by age, sex, race, education, geographic location, occupation, etc. An accrual rate should be estimated. If multiple institutions are involved, the proposal should include verification of the co-investigators' willingness to participate, and pertinent additional information regarding the cooperating institutions' staff qualifications, resources, research plans, including patient availability and data flow, as well as corresponding budget requirements.

3. In addition, if multiple institutions will be involved, a description of how implementation of the trial will be standardized across participating centers. Items that should be addressed include, but are not limited to:
a) training to standardize the diagnosis, enrollment (inclusion/exclusion criteria) and treatment of subjects;
b) programs to standardize data management and confidentiality; and
c) procedures to ensure patient safety. If preliminary data are not available, the proposal should include a pilot phase to validatethese items.

4. Any known or potential complications should be described, along with the techniques and procedures to monitor any adverse events.

5. A willingness to work cooperatively with the NIAMS and OAM staff in the implementation and conduct of the study should be indicated.

6. Applicants from institutions which have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. In such a case, a letter of agreement from either the GCRC Program Director or Principal Investigator could be included with the application.

REVIEW CONSIDERATIONS

General Considerations

Upon receipt, applications will be reviewed for completeness by the DRG and responsiveness by the OAM and NIAMS. Incomplete applications will be returned to the applicant without further

consideration. If the application is not responsive to the RFA, OAM and NIAMS staff will return the application to the applicant.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the National Advisory Council for NIAMS.

Review Criteria

All applications submitted in response to this RFA will be reviewed according to an explicitly-stated set of five review criteria recently adapted by the NIH: significance, approach, innovation, investigator (qualifications) and environment. Reviewers will consider these criteria when assigning a single overall score to each application. A detail description of these criteria can be accessed on the World Wide Web at:
http://grants.nih.gov/grants/peer/rgacriteria.htm.

In addition, reviewers will consider the following issues, which are specific to this RFA:

o Appropriateness of the proposed budget and duration in relation to the proposed research;
o Overall feasibility and the likelihood of achieving the clinical trial goals and the potential for a successful trial.
o Pilot phase experience including evidence of patient accession and retention.
o Adequacy of the statistical features of the study including sample size projections and power estimates, methods of analysis, and the use of sequential analyses of data.
o Logistical aspects of the project including plans for patient recruitment, quality control of data, proper randomization and masking procedures, data collection, data management and, reporting and plans for defining access and restriction to data. If preliminary data are not available, the proposal should include a pilot phase to validate these items.
o Availability of suitable subjects for the clinical trial and the likelihood of participation through to completion of the follow-up.
o Adequacy of ethical and human safety issues, including current Institutional Review Board (IRB) human subjects approval(s).

o Adequacy of plans to include subjects from both genders, and from minority groups and subgroups as appropriate for the scientific goals of the proposed research. Plans for the recruitment and retention of subjects also will be evaluated.

In order to ensure patient safety, the independence, proposed composition (in general terms, not specific individuals), and procedures of the DSMC will be considered among the review criteria. In addition, the initial review group will evaluate the proposed gender and minority composition of the study population in relation to the scientific issues being addressed during scientific and technical merit reviews.

For the initial review of the individual institutions participating in a multicenter clinical trial as a participating center, the review criteria will include:
o Commitment of the institution and staff to a collaborative protocol and to the success of the study.
The inclusion of letters of agreement from collaborating investigators, countersigned by the appropriate institutional official is necessary.
o Qualifications and the experience of the investigators and the availability of suitable subjects for the trial and the likelihood of full participation.
o Adequacy of the facilities including technical resources and space.
o Appropriateness of the local organization and administration.
o Appropriateness of the budget.
o Adequacy of methods for data collection and reporting from each institution
o Adequacy of ethical and human safety issues, including current Institutional Review Board (IRB) human subjects approval(s).

AWARD CRITERIA

The anticipated date of award is April 1, 1998

Award criteria are:
o responsiveness to goals and objectives of RFA
o priority score
o availability of funds

Award of funds for the approved future years of the grant will require submission of a noncompeting continuation application, PHS form 2590, to NIAMS at least two months prior to the

anniversary date of the award. Failure to supply the PHS form 2590 in a timely manner will impede release of outyear funding.

Letter of Intent Due: August 17, 1997
Application Receipt Date: September 19, 1997
Review by Initial Review Group: November-December, 1997
Review by Advisory Council: February 5-6, 1998
Anticipated Award Date: April 1, 1998

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquires regarding programmatic issues to:

Richard L. Nahin, Ph.D., M.P.H.
Program Officer
NIH Office of Alternative Medicine
9000 Rockville Pike
Bldg. 31, Room 5B-38
Bethesda, MD 20892-2182
Tel: 301-496-4792
Fax: 301-480-3519
E-mail: NahinR@OD31EM1.OD.NIH.GOV

and

James Panagis, M.D., M.P.H.
Program Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building Room 5AS-37K - MSC 6500
Bethesda, MD 20892-6500
Tel: 301-594-5055
Fax: 301-480-4543
E-mail: panagisj@ep.niams.nih.gov

Direct inquiries regarding fiscal matters to:
Vicki L. Mauer
Grants Management Specialist
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building Room 5AS.49A - MSC 6500
Bethesda, MD 20892-6500
Tel: 301-594-3504
FAX: 301-480-5450
E-mail: maurerv@ep.niams.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.213 (OAM) and 93.846 (NIAMS). Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR Parts 52 and 45 CFR Part 74 [and Part 92 when applicable for State and Local governments]. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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